

Role of Surgery in the Management of Primary Lymphoma of the Gastrointestinal Tract

MICHAEL M. LAW, MD, SUSAN B. WILLIAMS, MD, AND JAN H. WONG, MD

From the Division of Surgical Oncology, Jonsson Comprehensive Cancer Center, University of California at Los Angeles (UCLA) School of Medicine, Los Angeles, California (M.M.L., S.B.W., J.H.W.); and the Department of Surgery, Sepulveda Veterans Administration Medical Center, Sepulveda, California (J.H.W.)

The role of surgery in the management of primary gastrointestinal lymphoma remains controversial. We retrospectively reviewed the management and outcome of 107 patients with the diagnosis of gastrointestinal lymphoma treated at the UCLA Medical Center during the period 1956–1990. Sixty-four patients underwent surgical exploration at the UCLA Medical Center; 35 of these underwent resection for cure. Sixteen of these 35 patients received no postoperative adjuvant therapy. Twenty-nine patients underwent palliative or “noncurative” resection. There were five postoperative deaths (mortality rate 8%). The overall morbidity rate was 48%. There were 3 perforations in a total of 53 patients receiving multiagent chemotherapy. Five-year actuarial survival was as follows: 59% for curative resection alone, 51% for curative resection plus adjuvant therapy, and 28% for “noncurative” resection ($P < 0.05$). Multivariate analysis revealed that stage of disease ($P < 0.01$) and resection for cure ($P < 0.05$) were independent predictors of survival. These results suggest that patients undergoing resection for cure have improved survival. The apparent low risk of perforation during chemotherapy, along with the considerable risk of morbidity and mortality associated with operation, suggests that a policy of debulking large tumors prior to chemotherapy is unwarranted.

© 1996 Wiley-Liss, Inc.

KEY WORDS: chemotherapy, stomach, small bowel, adjuvant therapy

INTRODUCTION

Primary lymphoma of the gastrointestinal tract is an unusual disease in which the optimal management strategy has not been clearly defined. The role of the surgeon in the management of the patient with lymphoma is usually confined to either diagnostic and/or staging procedures. However, when lymphoma appears to arise primarily from the gastrointestinal tract, the rationale for surgical intervention may change to therapeutic. Some investigators maintain that exploration is essential in assessing the extent of disease in order to plan appropriate therapy. In those individuals with apparently localized gastrointestinal lymphoma, resection of the involved gastrointestinal segment may be considered the primary treatment and potentially curative [1–10]. Surgical resection and/or debulking in individuals with more extensive disease may

reduce the risk of bleeding or perforation during the administration of chemotherapy and/or radiation therapy.

However, the true therapeutic value of surgical intervention in the treatment of gastrointestinal lymphoma remains controversial. Some investigators [7,11] have recommended surgical resection alone as the primary treatment in patients with resectable disease. Others [1,3,8] have reported that the addition of postoperative radiation appeared to improve the 5-year survival of patients with gastric lymphoma who have undergone “curative” resection, while Rosen et al. [7] have questioned

Accepted for publication November 5, 1995.

Address reprint requests to Dr. Jan H. Wong at his current address: Department of Surgery, University of Hawaii School of Medicine, 1356 Lusitania St., 6th Floor, Honolulu, HI 96813.

the value of adjuvant radiation in this setting. Still others [4,6,12,13] have described improved survival in patients receiving adjuvant chemotherapy with or without radiation therapy. Despite the apparent value of surgical resection in the management of gastrointestinal lymphoma, some reports have been unable to substantiate a poorer outcome for patients treated only with chemotherapy and radiation therapy [14], chemotherapy alone [11], or in certain instances, radiation therapy alone [15].

This investigation was undertaken to further examine the role of surgery in the management of primary lymphoma of the gastrointestinal tract. Our results suggest that patients undergoing surgical resection with curative intent have improved survival. The low risk of perforation during chemotherapy, as well as the high morbidity and mortality associated with surgery, argues against routine debulking of extensive, unresectable disease.

MATERIALS AND METHODS

During the 34 year period between 1956 and 1990, 120 patients with primary lymphoma of the gastrointestinal tract were seen at the UCLA Medical Center. Patients in whom the primary site was not clearly gastrointestinal, those with a questionable diagnosis of lymphoma, and individuals with the diagnosis of acquired immunodeficiency syndrome (AIDS) or infection with the human immunodeficiency virus (HIV) were excluded from analysis. One hundred and seven patients met these inclusion criteria and form the basis of this analysis. The medical records of these individuals were retrospectively reviewed.

Patients were staged utilizing the modified Ann Arbor staging system [16] in which Stage IE represents disease confined to a single extralymphatic site; Stage IIE, disease that extends to a regional lymph node basin; Stage IIIE, disease that extends to both sides of the diaphragm; and Stage IVE, diffuse or disseminated disease. Staging was based upon findings at the time of operation as well as the results of diagnostic testing. These most commonly included endoscopy, contrast radiographs of the upper gastrointestinal tract, and computed tomography. Due to the broad time frame of this analysis, no standard treatment regimen was utilized in the management of these patients and individual treatment plans varied substantially. Treatment modalities included surgical resection for cure, in which complete tumor removal was attempted; palliative or "noncurative" surgical resection, to decrease the tumor burden or bypass obstruction; external beam radiation therapy; and various combinations of chemotherapy.

Ninety-seven patients (91%) were operated upon for gastrointestinal lymphoma, 64 of whom had their operative procedure performed at the UCLA Medical Center and had complete operative reports available for detailed analysis. Thirty-five patients were operated on with "curative" intent, while the remaining 29 patients underwent

noncurative resections, either for diagnosis or palliation. The surgical procedures performed were dependent upon the location of the primary tumor, and included subtotal (62%) or total (38%) gastrectomy for primary gastric lymphoma, and resection of the involved segment of bowel and adjacent tissue for intestinal lymphoma. Noncurative operative procedures included debulking operations, resectional biopsies, and procedures to bypass intestinal obstruction. Surgical mortality was defined as death within 30 days of operation. Morbidity and mortality was calculated only for the 64 patients operated on at the UCLA Medical Center. Overall, 53 patients received chemotherapy, and 54 were treated with radiation therapy. The most frequently administered chemotherapy regimen was cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). External beam radiation was administered in doses ranging from 550 to 6,500 cGy (mean 3,130 cGy). Survival curves were calculated by the method of Kaplan and Meier [17] and statistical differences were determined by the log-rank test.

RESULTS

Age, Sex, and Presentation

The patient population ranged in age from 5 to 92 years (mean 52 years). Fifty-five percent of the patients were male. While the sex distribution was essentially equal for patients with gastric lymphoma, there were twice as many males in the intestinal lymphoma group. The stage at presentation was almost equally divided between those presenting with localized disease, those with localized disease with regional nodal involvement, and those with disseminated disease. Thirty-two patients (30%) presented with Stage IE disease, 35 patients (33%) with Stage IIE disease, and 33 patients (31%) with Stage IVE disease. In six individuals the stage could not clearly be determined.

Fifty-seven percent of patients in this series had gastric lymphomas. The second most common site was the small bowel (31%). Table I summarizes the primary sites of involvement. Patients most commonly presented with abdominal pain (78%), weight loss (47%), bleeding (29%), and fatigue (22%). Presenting symptoms are summarized in Table II. Some variation in the presenting symptoms was noted between individuals with primary gastric lymphoma and individuals whose lymphoma arose from other sites in the gastrointestinal tract. Bleeding, the presence of a palpable mass, and night sweats were more common presentations of intestinal lymphoma, while weight loss, fatigue, and early satiety were more common complaints among individuals with primary gastric lymphoma.

Histopathology

A number of histologic classifications have been proposed and employed for non-Hodgkin's lymphomas. The

TABLE I. Distribution by Site of Primary Lymphoma of the Gastrointestinal Tract

Site	No. of patients	Percent (%)
Stomach	61	57
Small bowel	33	31
Ileum/cecum	9	8
Colon	2	2
Rectum	2	2
Total	107	100

TABLE II. Presenting Symptoms of Primary Gastric and Small Bowel Lymphoma

Symptom	Total (%)	Gastric (%)	Small bowel (%)
Pain	78	79	76
Weight loss	47	56	35
Fatigue	22	28	15
GI bleeding	29	21	39
Palpable mass	21	15	28
Anorexia	14	13	15
Early satiety	7	13	0
Vomiting	7	11	2
Night sweats	18	10	28
Obstruction	6	5	6

TABLE III. Operative Morbidity in Patients Undergoing Surgical Treatment of Primary Lymphoma of the Gastrointestinal Tract at UCLA

Complication	No. of patients
Wound infection	7
Pleural effusion	4
Fistula	3
Cholestasis/jaundice	3
Sepsis	2
Intraabdominal abscess	2
Pneumonia	2
Pulmonary embolism	2

long time period of this series reflects the evolution of this classification system [18–21]. The variable nature of classification systems used prevented an accurate analysis of histologic type and grade.

Surgical Treatment

The average duration of hospitalization in patients undergoing palliative or curative resection was 23 days (range 3–87 days). This included a mean of three intensive care unit days (range 0–58 days). The average transfusion requirement was three units of packed red blood cells. Table III summarizes the postoperative complications. Wound infection was the most common (11%), followed by pleural effusion (6%), fistula (5%), cholestasis/jaundice (5%), sepsis (3%), intraabdominal abscess (3%), pneumonia (3%), and pulmonary embolism (3%). Four-

TABLE IV. Multifactorial Analysis of Patients With Primary Lymphoma of the Gastrointestinal Tract

Prognostic variable	Univariate analysis	Multivariate analysis
Age	$P = 0.047$	$P = 0.171$
Gender	$P = 0.308$	~
Site of primary	$P = 0.248$	~
Stage of disease	$P < 0.001$	$P < 0.001$
Resection for cure	$P = 0.003$	$P = 0.022$

teen patients (22%) required reoperation for postoperative complications. There were five postoperative deaths (mortality rate 8%).

Chemotherapy

Analysis of the efficacy and morbidity of specific chemotherapeutic regimens was not carried out, as there was great variability in drug combinations and administration protocols. Instead we examined chemotherapy as a whole. Fifty-three patients were treated with a combination chemotherapy regimen, most commonly consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Twenty-eight patients received primary chemotherapy without resection, while 25 received postoperative adjuvant chemotherapy. Complications of chemotherapy were common, including some form of cytopenia (19%), severe nausea and vomiting (15%), sepsis (11%), and perforation (6%). Two patients (4%) died secondary to septic complications of chemotherapy. Two of the three patients with gastrointestinal perforation during chemotherapy had underlying problems that could have contributed to the development of this complication. One patient presented with perforation prior to treatment, and perforated again after only two doses of chemotherapy. The other patient had coexistent Crohn's disease and an ileal perforation.

Survival

The following potential prognostic variables were evaluated by univariate analysis: age, gender, site of primary, stage of disease, and resection for cure (Table IV). Of these, only age, stage of disease, and resection for cure were found to have statistical significance ($P < 0.05$) as predictors of survival. In a multivariate analysis controlling for these factors (stepwise log-rank test), only stage of disease ($P < 0.001$) and resection for cure ($P = 0.022$) maintained prognostic significance.

The mean actuarial survival for all 107 patients was 104 months, with a median actuarial survival (50% mortality) of 42 months (Table V). Patients undergoing surgery for cure had a mean survival of 135 months and a median survival of 168 months. In contrast, those undergoing palliative surgery had a mean survival of 81 months and a median survival of only 24 months ($P = 0.004$). Median survival by stage was as follows: Stage I, 168

TABLE V. Actuarial Survival of Patient With Primary Gastrointestinal Lymphoma

	Median (months)	Mean (months)
All patients	42	107
Curative resection	168	135
Palliative resection	24	81
Stage I	168	140
Stage II	80	150
Stage IV	7	31

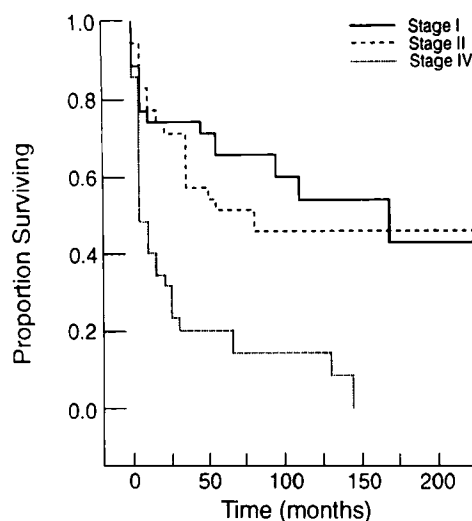


Fig. 1. Actuarial survival by stage of disease of patients with primary gastrointestinal lymphoma of the gastrointestinal tract. The survival differences are statistically significant ($P = 0.001$).

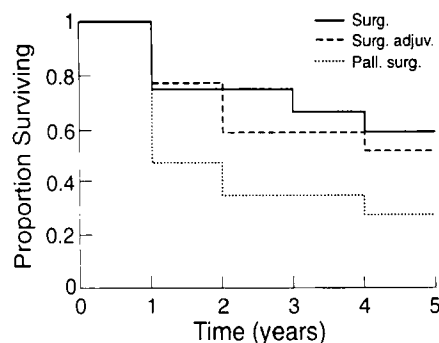


Fig. 2. Actuarial survival by treatment of patients with primary lymphoma of the gastrointestinal tract. The survival differences are statistically significant ($P = 0.05$).

months; Stage II, 80 months; and Stage IV, 7 months. These survival differences were statistically significant by log-rank analysis ($P = 0.0001$). Survival by stage is presented graphically in Figure 1.

Five-year actuarial survivals were calculated for the 35 patients who underwent resection for cure at the UCLA Medical Center (Fig. 2). Those who did not receive post-

operative radiation or chemotherapy ($n = 16$) had a 5-year actuarial survival of 59%. Patients who received postoperative adjuvant chemotherapy and/or radiation therapy ($n = 19$) had a 5-year actuarial survival of 51%. Twenty-nine patients undergoing "noncurative" resection had a 5-year actuarial survival of 28%. The differences between each of these treatment groups were statistically significant ($P < 0.05$, log-rank test).

DISCUSSION

The prevailing philosophy in the management of primary gastrointestinal lymphoma has been to attempt resection when the disease is judged to be resectable and the patient is felt to be an acceptable surgical risk. This strategy is based upon a number of reports [2,6,8–10] suggesting that individuals who undergo resection of their disease do better than their unresected counterparts. In those individuals who are not completely resectable, excision of the involved segment of bowel may prevent bleeding and perforation, believed to be associated with intensive chemotherapy and radiation therapy [9,10]. The purpose of this investigation was to further examine the role of surgical resection in the management of primary gastrointestinal lymphoma.

Our results support the concept that surgical resection is associated with a longer survival. This observation may reflect a selection bias, because patients with lower stage disease are more likely to be candidates for curative surgery, and patients with localized disease historically and theoretically have a better outcome [7,10,22]. However, we have assessed the impact of a number of potential prognostic variables by multivariate analysis and found resection for cure to be an independent predictor of survival.

Patients receiving adjuvant radiation and/or chemotherapy following surgery did not demonstrate any survival benefit over those treated with surgery alone. These patients, in fact, demonstrated poorer survival than those individuals treated with surgery alone. This observation is somewhat surprising in that lymphoma is generally regarded to represent a systemic disease of the hematopoietic system, and thus there is a clear rationale for the administration of adjuvant therapy. Our findings are in contrast to several other studies in which postoperative radiation or chemotherapy produced a marked survival difference. Shiu and colleagues [3] have reported that the addition of radiation therapy increased 5-year survival in gastric lymphoma from 33% to 67%, with the best results in patients receiving high-dose treatment. This group later reported that multiagent chemotherapy was as effective as radiation in this setting, and argued that high-risk patients should receive both [6]. Mittal et al. [4] have found that the combination of postoperative radiation and chemotherapy is associated with better survival than surgery plus radiation, or either treatment alone. Other investigators

[1,15] have noted improved survival statistics in patients receiving adjuvant therapy.

However, Rosen and colleagues [7] found that adjuvant radiation therapy did not improve survival in patients undergoing curative or palliative resection. Gobbi et al. [11] have similarly been unable to demonstrate a benefit of adjuvant chemotherapy and/or radiation therapy over surgery alone. The lack of improvement in survival in patients receiving adjuvant therapy may indicate that these cases truly represent localized disease that is completely removed at surgery. Alternately, it is possible that radiation and chemotherapy are ineffective in controlling residual disease in this group of patients. It seems clear from the literature, however, that both treatment modalities are active against gastrointestinal lymphoma, and thus this explanation is unlikely. Lastly, the decision to administer postoperative adjuvant therapy may have been based, in some cases, on an operative impression that residual disease remained after attempted "curative resection." If so, the group receiving postoperative adjuvant therapy may have had, on average, more advanced disease than the group treated with surgery alone.

In order to determine if our grouping of all adjuvant treatments together in the survival analysis masked the benefit of one particular regimen, we determined separate 5-year survivals for patients receiving postoperative chemotherapy, radiation therapy, and combination therapy. There were no significant survival differences between these groups.

The benefits of surgical resection must be weighed against the potential for operative complications, which appears to be considerable in patients with gastrointestinal lymphoma. The operative mortality rate for all surgically treated patients was 8%. Other studies [1,9–11,14,23] have described surgical mortality rates of 7–16%. Surgical morbidity was also similar to that reported in other series. This considerable morbidity and mortality reflects, in part, the fact that many of these patients are medically and nutritionally debilitated at the time of resection. As well, the immunosuppressive nature of lymphoma may contribute to the increased susceptibility of these patients to potentially lethal infectious complications, such as pneumonia, intraabdominal abscess, and sepsis.

The possibility of perforation and bleeding in gastrointestinal lymphomas treated primarily with chemotherapy and/or radiation therapy is a source of great concern and ongoing debate. In this study, the perforation rate during chemotherapy was 6% (3/53). This includes two patients whose perforations may be related to conditions that predated the complication: perforation at initial presentation in one patient and underlying Crohn's disease in the other. If these two cases are excluded, there was only one de novo perforation in more than 50 patients receiving multiagent chemotherapy, over half of which ($n = 28$) did not undergo prior resection. All perforations were

managed surgically, with no deaths attributable to the perforation.

Some investigators have described dire consequences of multiagent chemotherapy in unresected patients. Rackner et al. [10] reported two perforations in 15 patients, both of which were fatal. Fleming et al. [2] reported massive upper gastrointestinal hemorrhage in four of five patients treated primarily with CHOP chemotherapy. Several large series, however, have encountered neither of these complications in unresected patients. Maor et al. [14] treated 35 gastric lymphoma patients, most often with CHOP plus bleomycin, with no perforations or hemorrhage. Gobbi et al. [11] report a similar experience with 30 unresected patients. In a review of 17 original reports, Mittal et al. [4] found only three cases of perforation in radiated, unresected patients, and only one of these occurred during the course of treatment. Patients with gastrointestinal lymphoma may have an intrinsic risk of perforation and bleeding that is independent of cytotoxic therapy. Notably, the Mittal et al. review found 25 spontaneous perforations in 626 patients prior to any form of therapy. As well, surgical resection may not obviate the risk of these complications. Steward et al. [24] have reported seven instances of perforation and eight of hemorrhage in 36 resected patients with high-grade lymphomas.

Primary gastrointestinal lymphoma represents an unusual clinical entity. Surgical resection has generally been considered an integral part of the therapeutic approach to this disease. Our results suggest that individuals with localized lymphoma of the gastrointestinal tract undergoing "curative" resection do better than those with more extensive disease treated with multiagent chemotherapy and/or radiation therapy. Surgical resection with curative intent was an independent predictor of survival. The surgical morbidity and mortality rates were, as in other studies, considerable, and argue for careful evaluation of surgical risk in this frequently debilitated groups of patients. The risk of perforation and bleeding associated with chemotherapy and radiation therapy may be overemphasized. Considering the potential risks of surgery and the apparent low incidence of perforation and hemorrhage related to chemotherapy and radiation therapy, a policy of debulking extensive tumors prior to these therapies is probably unwarranted.

REFERENCES

1. Contreary K, Nance F, Becker W: Primary lymphoma of the gastrointestinal tract. *Ann Surg* 191:593–598, 1980.
2. Fleming I, Mitchell S, Dilawari R: The role of surgery in the management of gastric lymphoma. *Cancer* 49:1135–1141, 1982.
3. Shiu M, Karas M, Nisce L, et al.: Management of primary gastric lymphoma. *Ann Surg* 195:196–202, 1982.
4. Mittal B, Wasserman T, Griffith R: Non-Hodgkin's lymphoma of the stomach. *Am J Gastroenterol* 78:780–787, 1983.
5. Dragosics B, Bauer P, Radaszkiewicz T: Primary gastrointestinal non-Hodgkin's lymphoma: A retrospective clinicopathologic study of 150 cases. *Cancer* 55:1060–1073, 1985.

6. Shiu M, Nisce L, Pinna A, et al.: Recent results of multimodal therapy of gastric lymphoma. *Cancer* 58:1389-1399, 1986.
7. Rosen C, vanHeerden J, Martin J, et al.: Is an aggressive surgical approach to the patient with gastric lymphoma warranted? *Ann Surg* 205:634-640, 1987.
8. Hockey M, Powell J, Crocker J, Fielding J: Primary gastric lymphoma. *Br J Surg* 74:483-487, 1987.
9. Talamonti M, Dawes L, Joehl R, Nahrwold D: Gastrointestinal lymphoma: A case for primary surgical resection. *Arch Surg* 125:972-977, 1990.
10. Rackner V, Thirlby R, Ryan J: Role of surgery in multimodality therapy for gastrointestinal lymphoma. *Am J Surg* 161:570-575, 1991.
11. Gobbi P, Dionigi P, Barbieri F, et al.: The role of surgery in the multimodal treatment of primary gastric non-Hodgkin's lymphoma. *Cancer* 65:2528-2536, 1990.
12. Sheridan W, Medley G, Brodie G: Non-Hodgkin's lymphoma of the stomach: A prospective pilot study of surgery plus chemotherapy in early and advanced disease. *J Clin Oncol* 3:495-500, 1985.
13. Shepard F, Evans W, Kutas G, et al.: Chemotherapy following surgery for stages IE and IIE non-Hodgkin's lymphoma of the gastrointestinal tract. *J Clin Oncol* 6:253-260, 1988.
14. Maor M, Maddux B, Osborne B, et al.: Stages IE and IIE non-Hodgkin's lymphoma of the stomach: Comparison of treatment modalities. *Cancer* 54:2330-2337, 1984.
15. Weingrad D, Decosse J, Sherlock P, et al.: Primary gastrointestinal lymphoma: A 30-year review. *Cancer* 49:1258-1265, 1982.
16. Rosenberg S: Validity of the Ann Arbor staging classification for the non-Hodgkin's lymphomas. *Cancer Treat Rev* 61:1023-1027, 1977.
17. Kaplan E, Meier P: Non-parametric estimations from incomplete observations. *J Am Stat Assoc* 53:457-481, 1958.
18. Rappaport H: Tumors of the hematopoietic systems. In "Atlas of Tumor Pathology." Washington, DC: U.S. Armed Forces Institute of Pathology, 1966:97-161.
19. Gérard-Marchant R, Hamlin I, Lennert K, et al.: Classifications of non-Hodgkin's lymphomas. *Lancet* 2:406-408, 1974.
20. Lukes R, Collins R: New approaches to the classification of lymphomata. *Br J Cancer* 31(Suppl II):1-28, 1975.
21. The Non-Hodgkin's Lymphoma Pathologic Classification Project: National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas: Summary and description of a working formulation for clinical usage. *Cancer* 49:2112-2135, 1982.
22. Azab M, Henry-Amar M, Rougier P, et al: Prognostic factors in primary gastrointestinal non-Hodgkin's lymphoma. *Cancer* 64: 1208-1217, 1989.
23. Jones R, Willis S, Innes D, Wanebo H: Primary gastric lymphoma: Problems in staging and management. *Am J Surg* 155:118-123, 1988.
24. Steward W, Harris M, Wagstaff J, et al.: A prospective study of the treatment of high-grade histology non-Hodgkin's lymphoma involving the gastrointestinal tract. *Eur J Cancer Clin Oncol* 21:1195-1200, 1985.